

Modeling and Simulation of Pharmacokinetics and Pathophysiology: Applications in Drug Development

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Authors: Tomohisa Nakada

I have the following financial relationship to disclose for our presentation contents.

- Employee : Mitsubishi Tanabe Pharma Corporation

1. Quantitative Analysis of Creatinine Changes by Renal Transporter Inhibition

- Nakada T, Kudo T, Kume T, Kusuhara H, and Ito K. *Drug Metabolism and Pharmacokinetics* (2018) 33:103-110.
- Nakada T, Kudo T, Kume T, Kusuhara H, and Ito K. *Drug Metabolism and Pharmacokinetics* (2019) 34:233-238.

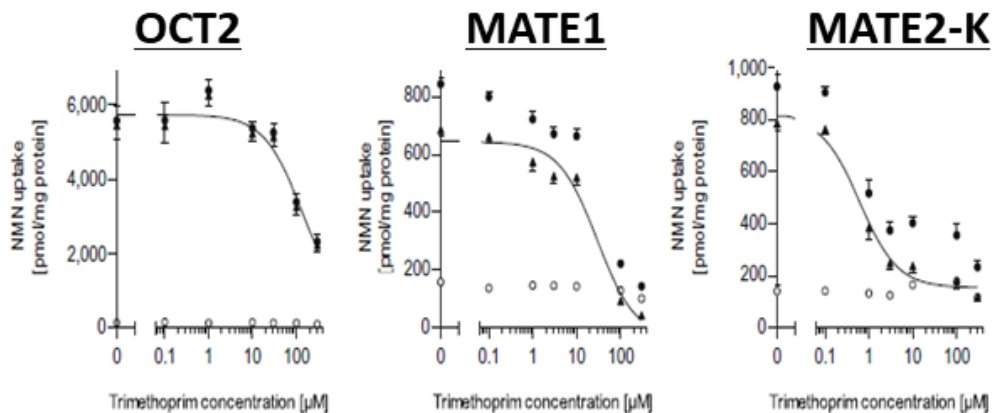
2. Applications of Systems Models in Drug Development

- **An increase in serum creatinine (SCr) after administrations of NME could lead to:**
 - dose reduction
 - termination of the clinical program
(its potential association with acute renal impairment)
- **Drugs have been found SCr elevation without affecting other markers for renal function:**

Important issue to understand the mechanism underlying SCr rise

In vitro study

Renal TP Inhibition of Trimethoprim

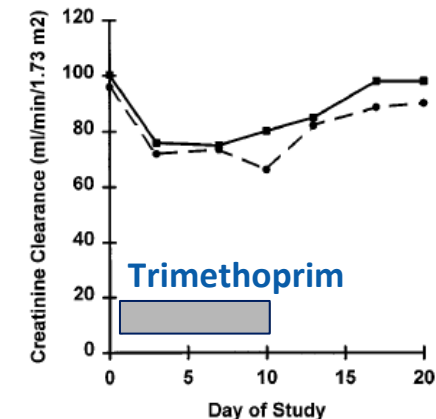
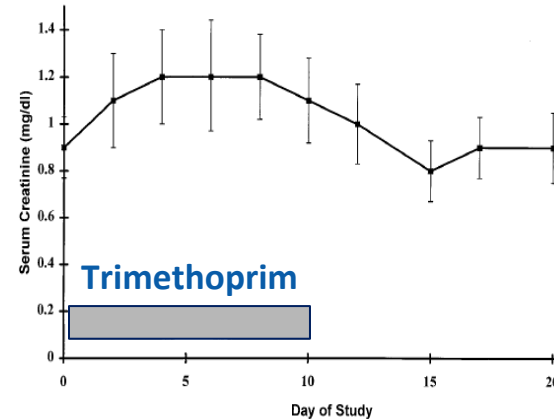


Muller et al., Br J Clin Pharmacol 76: 787-96 (2015).

Phase I study

Serum creatinine (SCr)

Creatinine clearance (CL_{cre})



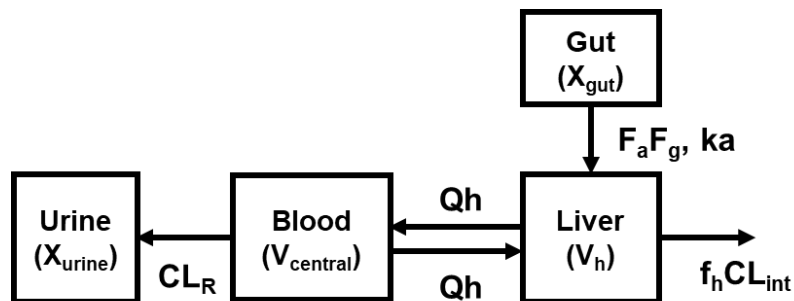
Naderer et al., Antimicrob Agents Chemother 41: 2466-70 (1997).

To what extent TPs inhibitions contribute to SCr/CL_{cre} changes?

Physiologically-Based Pharmacokinetic (PBPK) Model

PBPK model

Mathematical model to express PK-time profiles in each tissue



**Fitting
Simulation**

Physiological inputs

- Liver volume
- Hepatic blood flow
- Body weight

Drug profile inputs

- Protein unbound fraction in blood
- Blood-to-plasma conc. ratio
- Renal clearance
- etc.

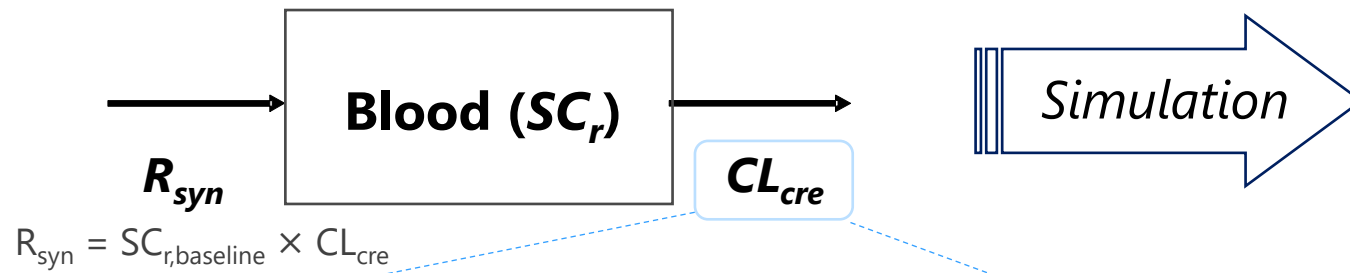
Dosing regimen

- Route
- Dose regimen

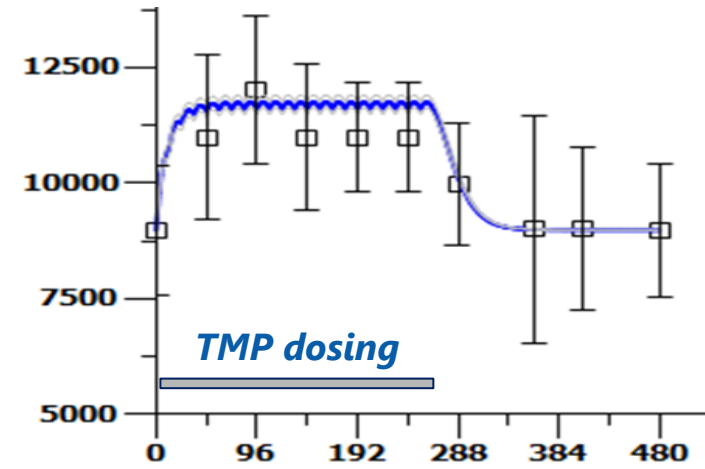
Model-Based Simulation for Creatinine Changes

—Inhibitory Effects of TMP on Renal Transporters

Creatinine Model

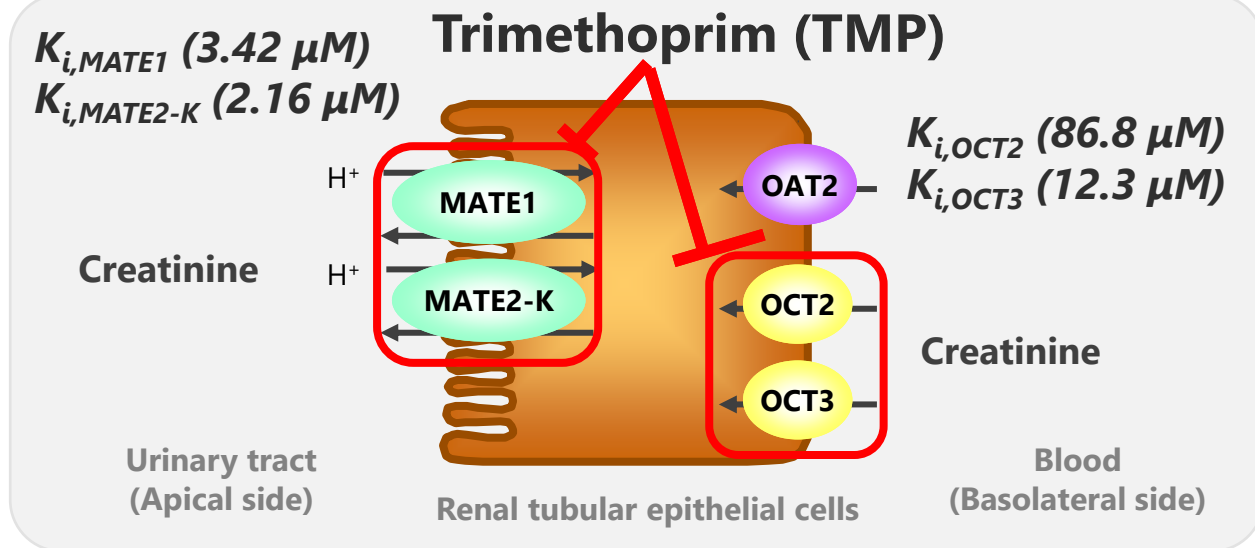
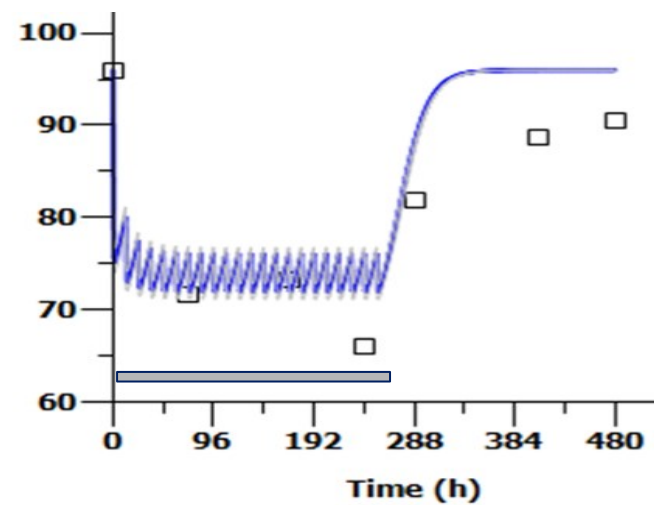


Serum creatinine (SCr)



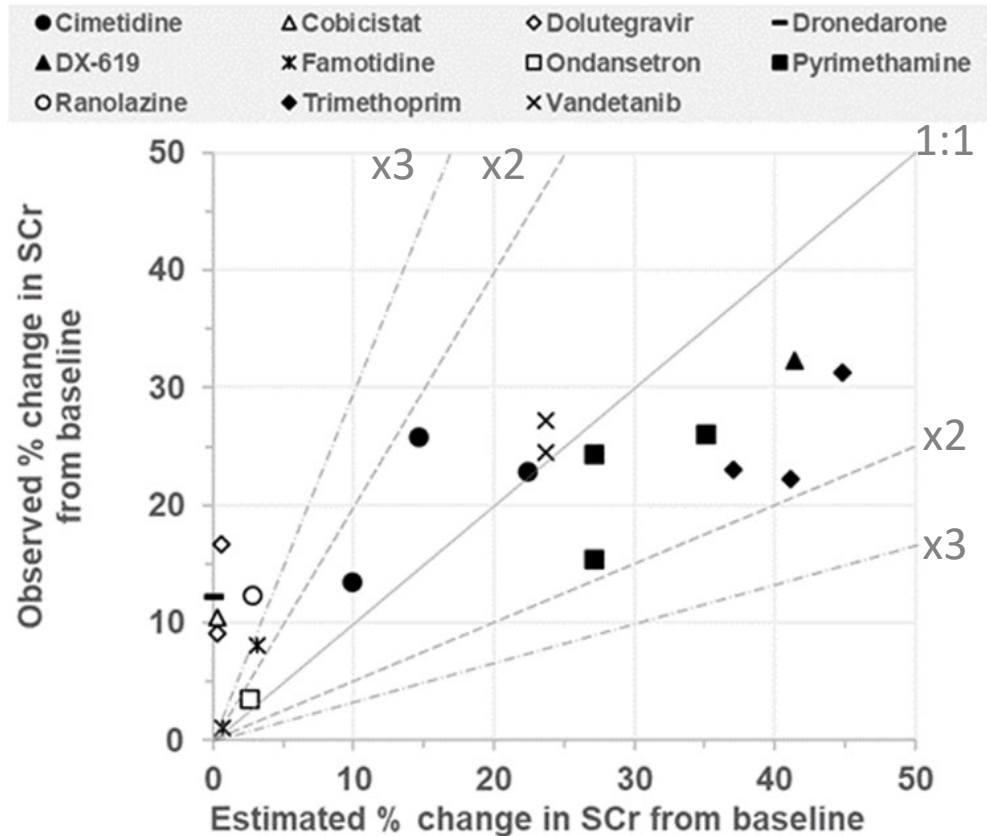
□ Observed
— Predicted

Creatinine clearance (CL_{cre})

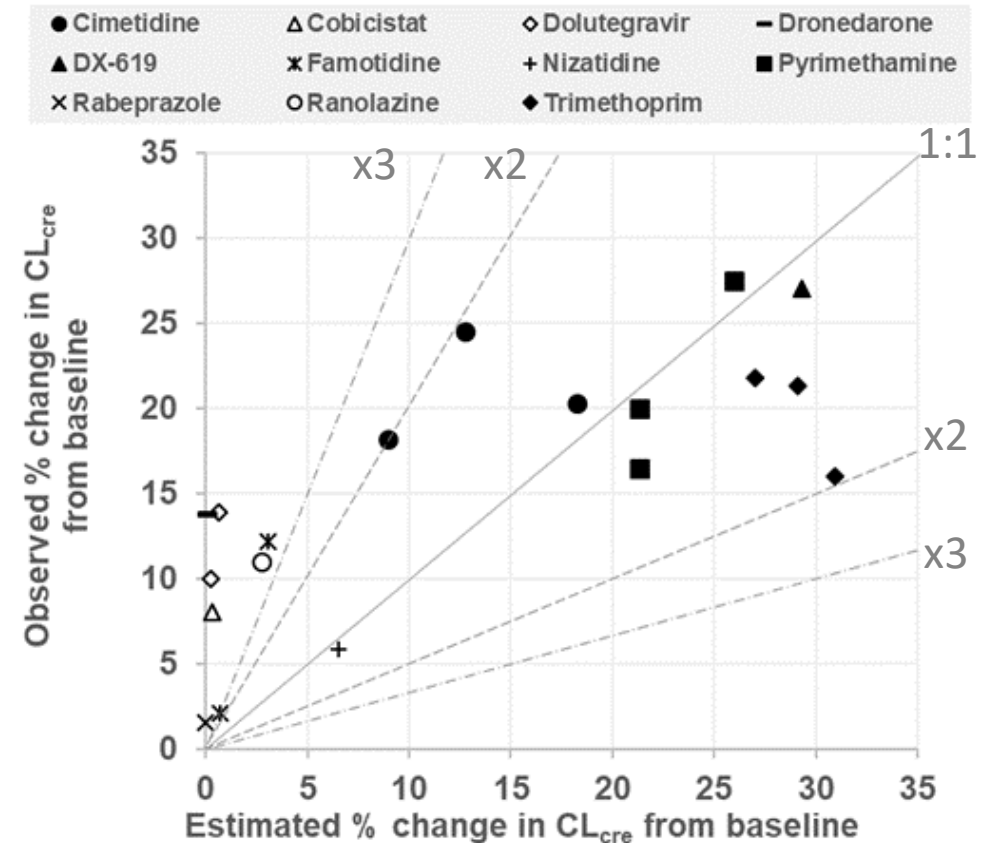


Estimated SCr and CL_{cre} from $C_{max,u}$ of Test Drugs

%Change in SCr vs Baseline



%Change in CL_{cre} vs Baseline



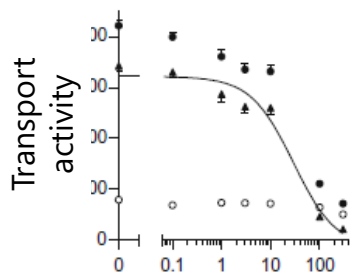
Most cases of estimates <2 or 3-fold of observed values

Possible Clinical Application of Creatinine Modeling

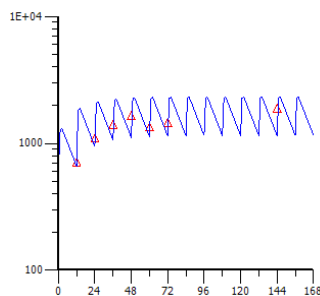
Pre-clinical

Early Clinical

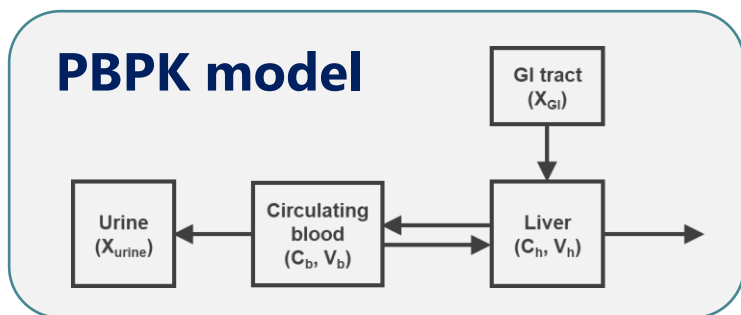
In vitro TP Inhibition
(IC_{50} , K_i)



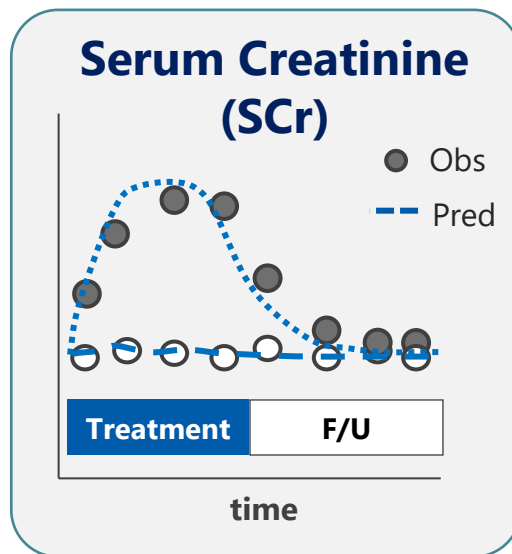
NME PK and SCr Change
In Healthy Subjects (HS)



PBPK model



Serum Creatinine (SCr)



SCr elevated in HS

DDI Study with a Renal TP Substrate

Yes

No

Further Investigation on Possible Renal Impairment

1. Quantitative Analysis of Creatinine Change by Renal Transporter Inhibition

2. Applications of Systems Models in Drug Development

a) Comparative Evaluation for MR Antagonists-Induced Hyperkalemia Potential with a QSP Model

Nakada T, Rengaswamy M, Dasika K, Kumar R, and Saito R. *J Pharmacokinet Pharmacodyn* (2017) 44:S116 W-044.

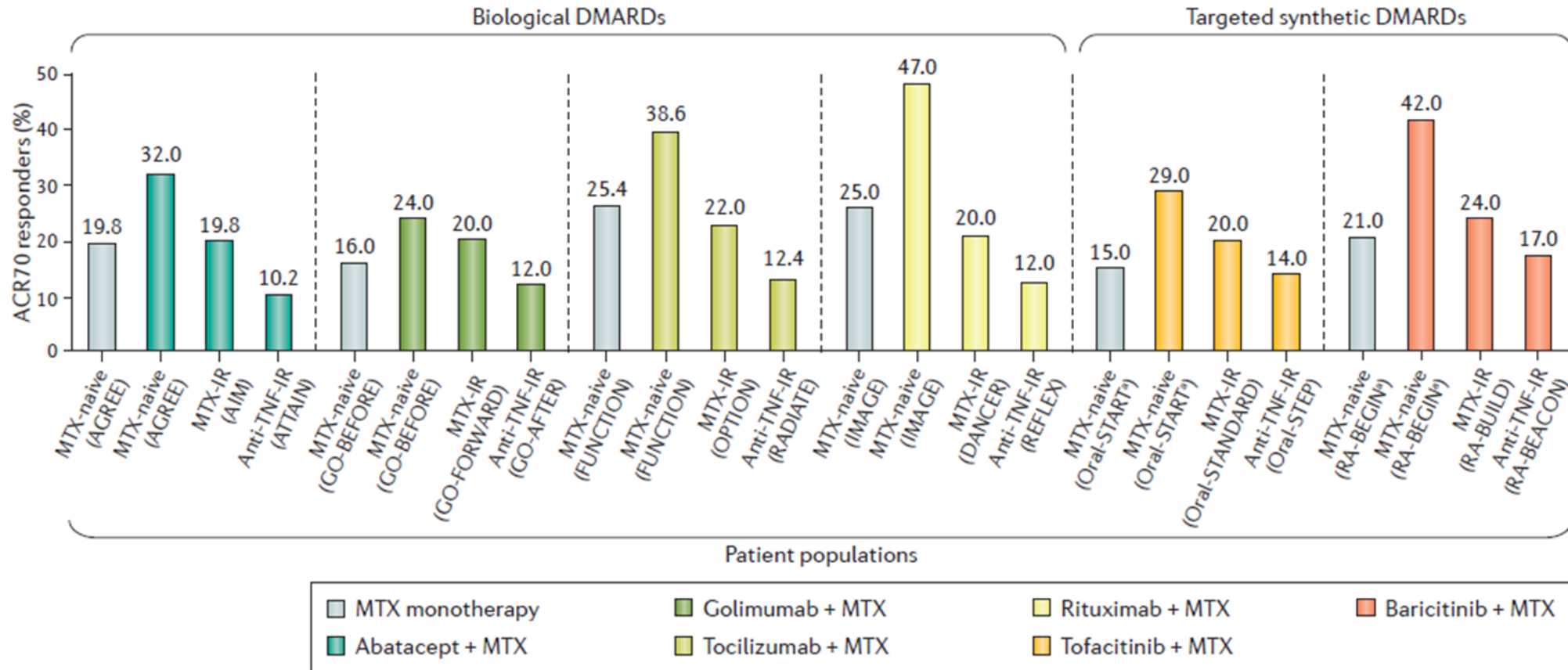
b) Mechanistic Analysis of SGLT1/2 Inhibition on Postprandial Hyperglycemia with a Systemic Glucose Dynamics Model

Mori-Anai K, Tashima Y, Nakada T, Nakamaru Y, Takahata T, and Saito R. *Biopharm Drug Dispos* (2020) 41:352-66.

c) Development of a Systems Model to Identify Baseline Cytokines on Rheumatoid Inflammation

Nakada T and Mager DE. *Clin Pharmacol Ther* (2021) 109:S5-88 PIV-052.

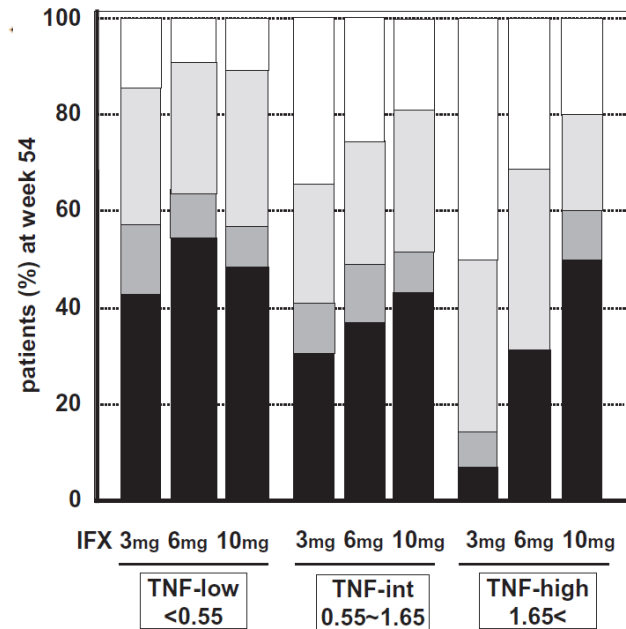
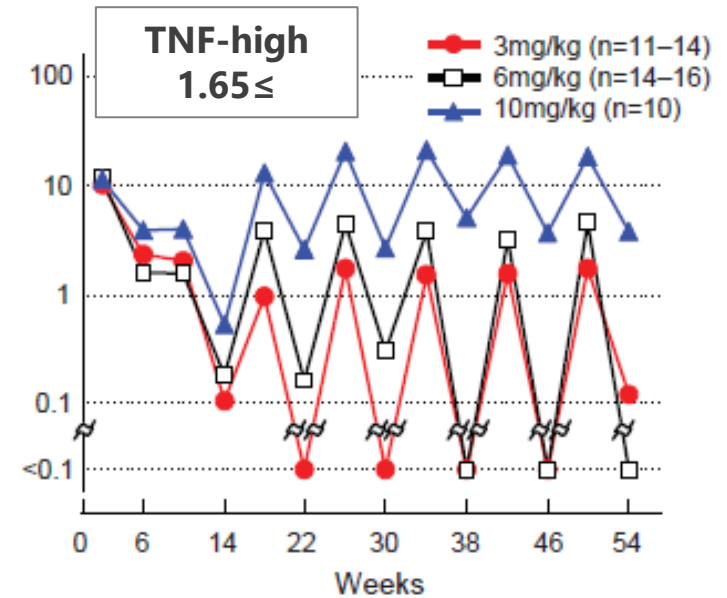
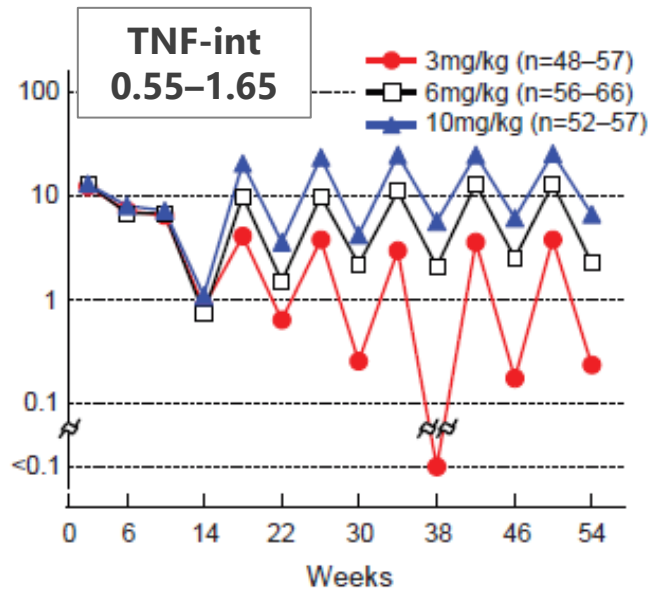
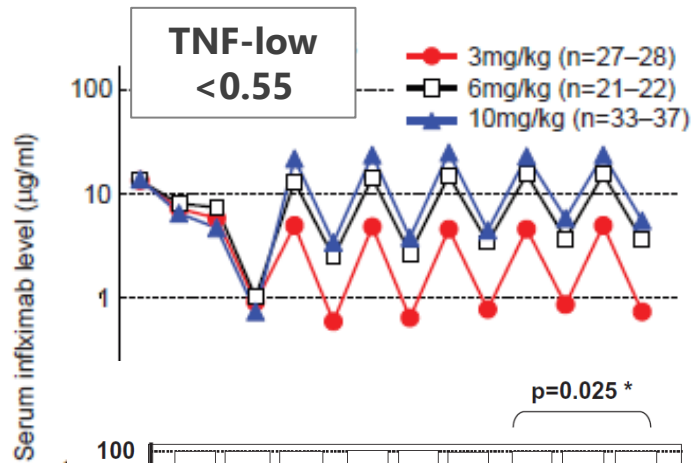
Treatments and Outcomes in Rheumatoid Arthritis (RA)



Smolen JS et al. Nature Rev Dis Primers (2018) 8:18001.

Despite recent therapeutic advances of RA treatment, only a minority of patients led to therapeutic success

RISING Study — Infliximab PK and Outcomes

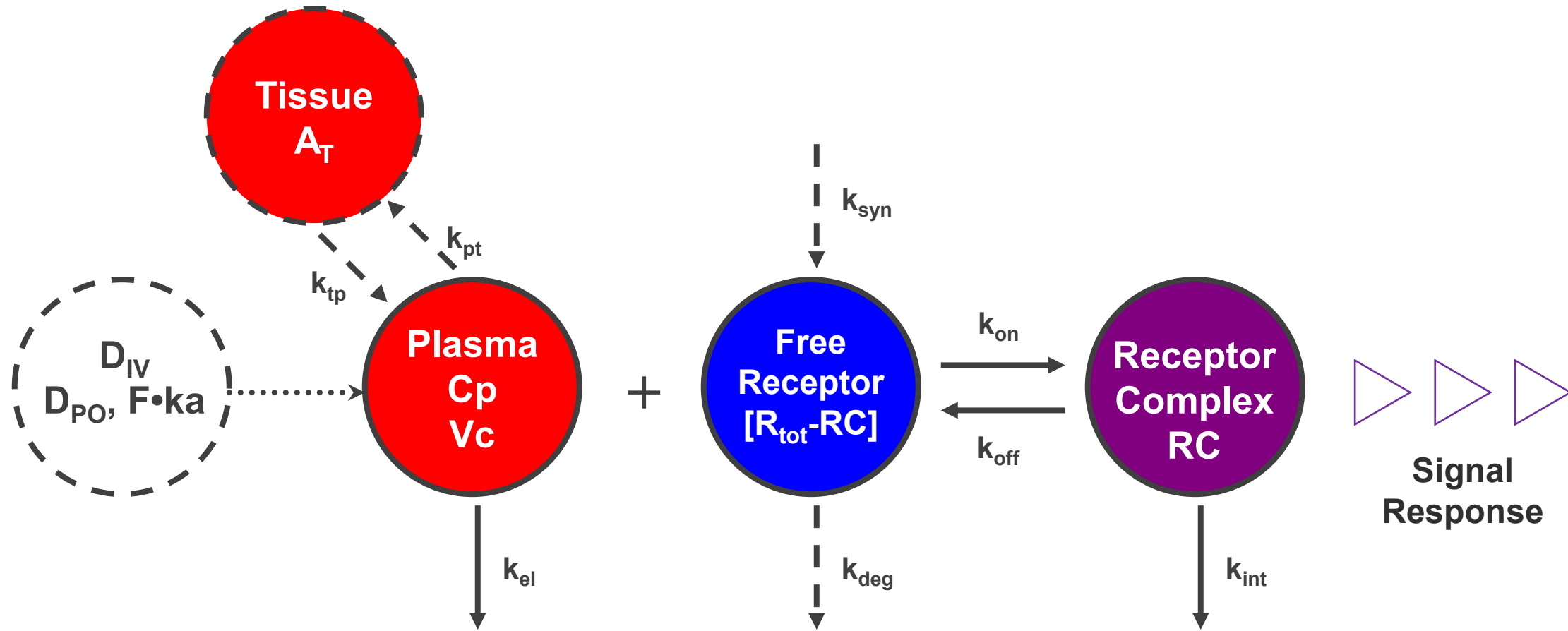


Takeuchi T et al. Ann Rheum Dis (2011) 70:1208-15.

TNF α baseline differences significantly associated with not only the PK but outcomes

DAS28 -CRP
 □ HDA □ MDA □ LDA ■ Remission

Target-Mediated Drug Disposition (TMDD)



Mager DE and Jusko WJ. J Pharmacokinet Pharmacodyn (2001) 28:507-32.

Acknowledgement

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Mitsubishi Tanabe Pharma

Creating hope for all facing illness.